I. REMARKS

Claims 1-3 and 5-21 are pending. Claims 3, 16, 17, and 19-21 are presently withdrawn. No amendments to the specification or claims are made at this time.

Claims 1, 2, 5-15 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over McIntyre et al. (Pharmacol. Ther., 74(2): 181-184 (1997)) in view of Del Soldato (WO 00/61537). This rejection is respectfully traversed.

Applicants agree with the Examiner that "McIntyre et al. do not teach attaching a nitrooxy tether to the drug [e.g., losartan] as instantly claimed" (Office Action, page 4).

Applicants also respectfully submit that attachment of the nitrooxy tether of Del Soldato to the losartan of McIntyre et al., as asserted by the Examiner, would not have resulted in the compounds of the presently claimed invention. While Del Soldato discloses that losartan is one of the many drugs that "can be used as precursors in formula (I) and (II)" of Del Soldato (see, e.g., page 41 of Del Soldato), the use of losartan as a precursor in formula (I) or (II) of Del Soldato would not result in the elected compound (i.e., compound 2 of the present application).

In particular, Applicants note that Del Soldato discloses compounds synthesized from a precursor drug and a precursor compound of B. For example, Del Soldato discloses compounds of formula I A-B-C-$N(O)_s$. In formula I, A = R-T_1 and R is a drug radical. Further, -B-C- is a linker bridging the -$N(O)_s$ group and A. B = (-T_B-X_2-T_{B1}-) and is an anti-oxidant moiety defined as a radical derived from a precursor molecule having anti-oxidant properties (i.e., which meets test 4 as disclosed in claim 1 and page 16 of Del Soldato). Examples of such anti-oxidant molecules are disclosed on pages 16-17

and claim 3 of Del Soldato. Meanwhile, C = ($-T_c$-Y) and is an aliphatic, aromatic, or heterocyclic spacer. As such, in contrast to the compounds of the presently claimed invention, Del Soldato discloses compounds that include a precursor drug and a precursor compound of B.

As another example, Example 10 of Del Soldato discloses the compound NCX2211, where a nitrooxy tether is attached to a compound "wherein the precursor [drug] is alendronic acid of formula (XIII) and the precursor of B is the ferulic acid (formula DII)" (Del Soldato, page 84). If losartan were substituted for alendronic acid in Example 10 of Del Soldato, the compound would include a precursor of B, such as ferulic acid, between the losartan and the nitrooxy tether. In contrast, compound 2 of Example 2 of the present application (i.e., the elected species) has the nitrooxy tether directly attached to the losartan compound.

Del Soldato also discloses that the compounds of formula I are useful in pathologies associated with oxidative stress and/or endothelial dysfunctions where known drugs show a lower activity and/or higher toxicity. See, e.g., the first full paragraph on page 7 of Del Soldato. As such, Del Soldato discloses that a $-ONO_s$ group linked to a drug through a linker having anti-oxidant activity improves the pharmacological profile in conditions of oxidative stress.

In contrast, the presently claimed invention discloses angiotensin II receptor blocker nitroderivatives able to release NO that have unexpectedly increased anti-hypertensive activity, anti-inflammatory activity, and anti-platelet activity, independent from the existence of conditions of oxidative stress. For example, Tables 2-4 in the

specification disclose increased anti-inflammatory activity, anti-platelet activity, and anti-hypertensive activity, respectively, of NO-losartan compounds of the presently claimed invention (including the elected species, compound 2 of Example 2) as compared to losartan. Table 2 discloses that NO-losartan of Example 4 was able to inhibit the accumulation of nitrites induced by lipopolysaccharide (LPS), in contrast to the lack of inhibition by losartan. Table 3 discloses that the NO-losartan of Examples 1 and 2 were able to substantially inhibit platelet aggregation induced by the aggregating agent U46619, a TxA_2 analog, while losartan showed only a weak effect. Table 4 discloses that the NO-losartan of Example 2 was able to induce a greater reduction in blood pressure levels as compared to losartan over the treatment period.

As McIntyre et al. and Del Soldato do not teach or suggest the compounds of the presently claimed invention or the unexpected advantages thereof, Applicants submit that the compounds of the presently claimed invention would not have been obvious to one of ordinary skill in the art over the disclosures of McIntyre et al. and Del Soldato, alone or in combination.

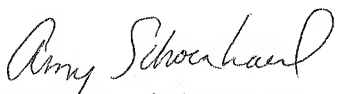
For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 5-15 and 18 under 35 U.S.C. § 103(a) over McIntyre et al. in view of Del Soldato.

II. CONCLUSION

For at least the above reasons, Applicant respectfully submits that this application is in condition for allowance and requests favorable action thereon. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicant's undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. **026220-00073**. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00073**.

Respectfully submitted,



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